INVESTIGATION OF INFLAMMATORY BREAST CANCER BIOLOGY AND POTENTIAL THERAPEUTIC APPROACHES

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Inflammatory breast cancer (IBC), the most lethal and least understood form of locally advanced breast cancer, manifests itself with inflammatory-like symptoms and is associated with increased vasculogenesis and local invasion of the lymphatic system. We used SUM-149, a human inflammatory breast cancer cell line, to characterize the unique IBC phenotype in vitro. Results showed that IBC cells use a different mode of invasion from other metastatic breast cancer cells and invade as tumor spheroids in a Matrigel matrix, similar to the tumor emboli seen in IBC pathology. As reported previously by van Golan et al., the IBC cells over expressed Rho and demonstrated more actin stress fibers. IBC cells also overexpressed E-cadherin and retained E-cadherin-based cell-cell adhesions in the tumor spheroids during invasion in 3-D Matrigel cultures (Hoffmeyer et al., 2005. *Cancer Cell Int.* 5:11). Current therapies for IBC include aggressive nonspecific anticancer treatments such as paclitaxel and doxorubicin that have drastic side-effects. To investigate the role of alternative targeted therapeutics that can be used in combination with current therapeutic options we are determining the efficacy of *Ganoderma lucidum* (Reishi) mushroom extract. Reishi mushroom is a traditional Chinese medicinal herb that has been shown to inhibit proliferation, adhesion, migration, and invasion of cancer cells. Resihi possesses biologically active compounds with polysaccharides that stimulate the immune system and triterpenes that demonstrate cytotoxicity against cancer cells at high concentrations. To test the hypothesis that the immunomodulatory, anti-inflammatory, and anti-cancer effects of Reishi may be effective against IBC progression and invasion, we tested the effect of whole Reishi extract on normal mammary epithelial (MCF-10A) and IBC (SUM-149) cell lines. Treatment with Reishi extract effectively inhibited proliferation of the IBC cell line SUM-149 but not the normal mammary epithelial cell line MCF10A. Vehicle-treated SUM-149 cells invaded a Matrigel matrix as tumor cell spheroids. Reishi treatment reduced cell-cell attachments and decreased invasion of IBC cells. Investigation of gene expression in response to Reishi using RT^2 profiler cancer pathway finder PCR arrays indicated that a total of 52% of tumorigenesis genes were down-regulated in IBC cells treated with the Reishi extract compared to those exposed to vehicle alone, including matrix-metalloproteinase-9 (MMP-9). Since MMPs are important for degradation of the extracellular matrix, we further investigated the effect of Reishi on MMP levels by gel zymography. Reishi at 0.5 mg/ml inhibited MMP-2 and MMP-9 levels compared to vehicle control. We conclude that Reishi inhibits IBC progression by reducing cell proliferation, preventing the formation of tumor emboli, and inhibiting invasion by reduced matrix MMP levels. Overall, these results demonstrate that Reishi extract is effective in inhibiting IBC progression and is a potential natural therapeutic for women suffering with this deadly disease.

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